

combining under fusing conditions yeast spheroplasts, said spheroplasts comprising a YAC having said xenogeneic DNA segment and a marker for selection, with embryonic stem cells of said animal, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker;

transferring said embryonic cells into a host blastocyst and implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develop to term to produce a chimeric animal carrying said xenogeneic DNA segment; and

mating said chimeric animal with an animal of the same species to produce said modified animal carrying said xenogeneic DNA segment.

75. (Amended) [The] A genetically modified non-human animal produced by [the] a method [according to Claim 72] which comprises interbreeding a first parent and a second parent, and recovering the progeny thereof, wherein the parents and progeny are selected from the group consisting of:

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain, and progeny homozygous for said modified genome;

first and second parents heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin heavy chain, and progeny homozygous for said modified genome;

a first parent heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin light chain, a second parent heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin heavy chain and progeny heterozygous for said

modified genome so as to be incapable of producing endogenous immunoglobulin heavy and light chains;

first and second parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains, and progeny homozygous for said modified genome;

a first parent hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin heavy chain, a second parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains, and progeny heterozygous for said modified genome so as to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a modified genome so as to be capable of producing xenogeneic immunoglobulin heavy chain;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin heavy chain) and progeny 1) homozygous for said modified genome and 2) homozygous for said modification of being incapable of producing endogenous immunoglobulin light and heavy chains and also hemizygous for the modification of being capable of producing xenogeneic immunoglobulin heavy chain;

a first parent hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light chain, a second parent heterozygous for a genome modified to be incapable of producing immunoglobulin heavy and light chains, and progeny heterozygous for said genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for said genome modified to be capable of producing xenogeneic immunoglobulin light chain;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light chain, and progeny 1) homozygous for said modified genome and 2) homozygous for said modification of being incapable of producing endogenous immunoglobulin light and heavy chains and also hemizygous for the modification of being capable of producing xenogeneic immunoglobulin light chain;

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for xenogeneic immunoglobulin heavy chain, a second parent heterozygous for genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for the modification of being capable of producing xenogeneic immunoglobulin light chain, and progeny homozygous and heterozygous for said genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for the modification of being capable of producing xenogeneic immunoglobulin light and heavy chains,

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny 1) homozygous for said modified genome, and 2) homozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains;

first and second parents homozygous for a genome modified to be incapable of producing endogenous

immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny homozygous for said modified genome:

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain, a second parent hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains,

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny 1) homozygous for said modified genome and 2) homozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains;

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain, a second parent hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain and hemizygous for the genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain and hemizygous for a genome

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modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny 1)
homozygous for said modified genome, and 2) homozygous for a genome more modified to be incapable of producing endogenous immunoglobulin light chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains.

Please add the following claims:

--79. A genetically modified non-human animal, wherein said genetic modification results in inability of said animal to produce endogenous antibodies in response to challenge by an antigen and wherein said genetic modification further permits said animal to produce non-endogenous antibodies in response to challenge by an antigen.

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80. The animal of claim 79 wherein said non-endogenous antibodies are human.

81. The animal of claim 79 that is a mouse.

82. A non-human animal modified to contain a YAC construct, said construct comprising an unarranged xenogeneic immunoglobulin locus, said animal being further modified so as to be incapable of producing endogenous antibodies.--

REMARKS

Applicants elect to prosecute the claims of Group IV, claims 16-26 and 75-78 drawn to a genetically modified non-human animal having a modified genome. It is believed that proposed new claims 79-82 fit squarely within this group.